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Short Communication

New-onset refractory status epilepticus following the ChAdOx1 nCoV-19 vaccine

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ABSTRACT

Coronavirus is a novel human pathogen causing fulminant respiratory syndrome (COVID-19). Developing an effective and reliable vaccine was emergently pursued to control the dramatic spread of the global pandemic. The standard stages for vaccine development were unprecedentedly accelerated over a few months. We report a case of new-onset refractory status epilepticus (NORSE) after receiving the first dose of the ChAdOx1 nCoV-19 vaccine. We attribute the occurrence of NORSE to the vaccine due to the temporal relationship and the lack of risk factors for epilepsy in the patient. This report adds to the literature a possible rare side effect of a COVID-19 vaccine and contributes to the extremely limited literature on potential neurological side effects of viral vector vaccines. Healthcare providers should be aware of the possibility of post-vaccination epilepsy. The patient had recurrent seizures that were refractory to conventional antiepileptic drug therapy with a dramatic response to immunotherapy with pulse steroids and plasmapheresis. This likely reflects an underlying autoimmune mechanism in the genesis of post-vaccination generalized seizures without fever. Further research is needed to probe and study the exact mechanism at a more molecular level.

1. Introduction

Coronavirus is a novel human pathogen causing fulminant respiratory syndrome (COVID-19) that was first identified in December 2019 as a cluster of cases with fatal pneumonia in Wuhan, China.(Zhu et al., 2020) In March 2020, the World Health Organization declared a worldwide pandemic and designated the disease taxonomy as COVID-19.(Dong et al., 2020) The disease is an acute severe respiratory syndrome with florid pulmonary manifestations and multi-organ involvement including cardiovascular, musculoskeletal, gastrointestinal, and neurological complications.(Huang et al., 2020) Developing an effective and reliable vaccine was emergently pursued to control the dramatic spread of the global pandemic. The standard stages for vaccine development were unprecedentedly accelerated over a few months. Inactivated or live-attenuated viruses as well as recombinant proteins and vectors technologies have been employed to develop the COVID-19 vaccine. In addition, new platforms such as RNA and DNA vaccines were also used for the first time in a licensed vaccine.(Li et al., 2020) We report a case of new-onset refractory status epilepticus (NORSE) after receiving the first dose of the ChAdOx1 nCoV-19 vaccine.

2. Case report

A 42-year-old female nurse of Black South African descent presented to the emergency department complaining of headache and subjective fever that started one day prior. During the assessment, the patient developed a rising epigastric sensation and experienced jamais vu for the first time in her life that rapidly evolved into her first-ever generalized tonic-clonic seizure. She was given 2 mg of lorazepam on two occasions that failed to abort the seizure and was eventually loaded with 1 g of phenytoin. Her seizure stopped, and she was stabilized and drowsy with post-ictal amnesia. She had no history of fever, infection, or any risk factor for epilepsy. She received the first dose of the ChAdOx1 nCoV-19 vaccine 10 days prior to presentation. Clinically, she was lethargic but fully conscious, alert, oriented, and her vital signs were stable. Her pupils were reactive bilaterally and she was following commands and moving all limbs freely. Her laboratory investigations were unremarkable including toxicology screens, infectious diseases serology, electrolytes, organ function tests, inflammatory markers, autoimmune serology, and vasculitis screen. In addition, cultures from blood, urine, stool, and respiratory secretions were unremarkable. COVID-19 PCR

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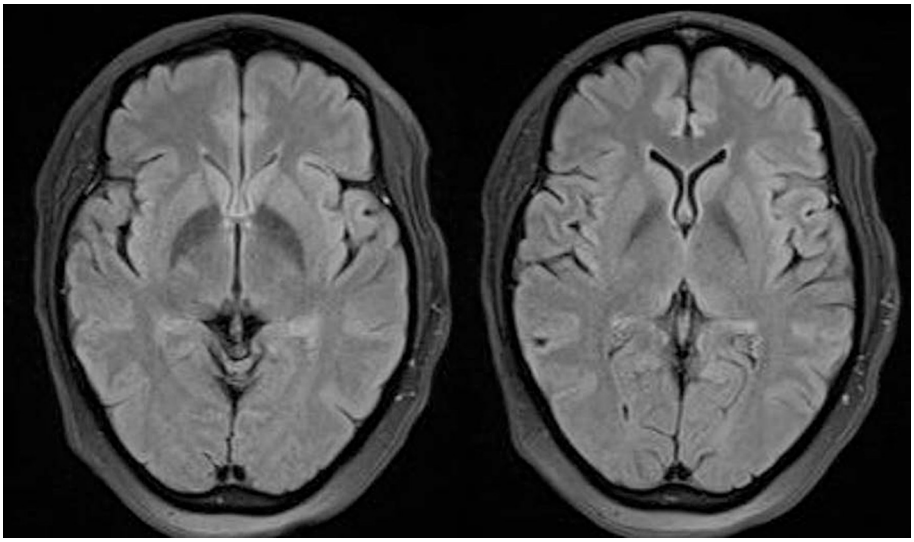

Fig. 1. Brain MRI showed a subtle increase in the signal on FLAIR images at bilateral hippocampi and insula that was correlating with postictal changes.

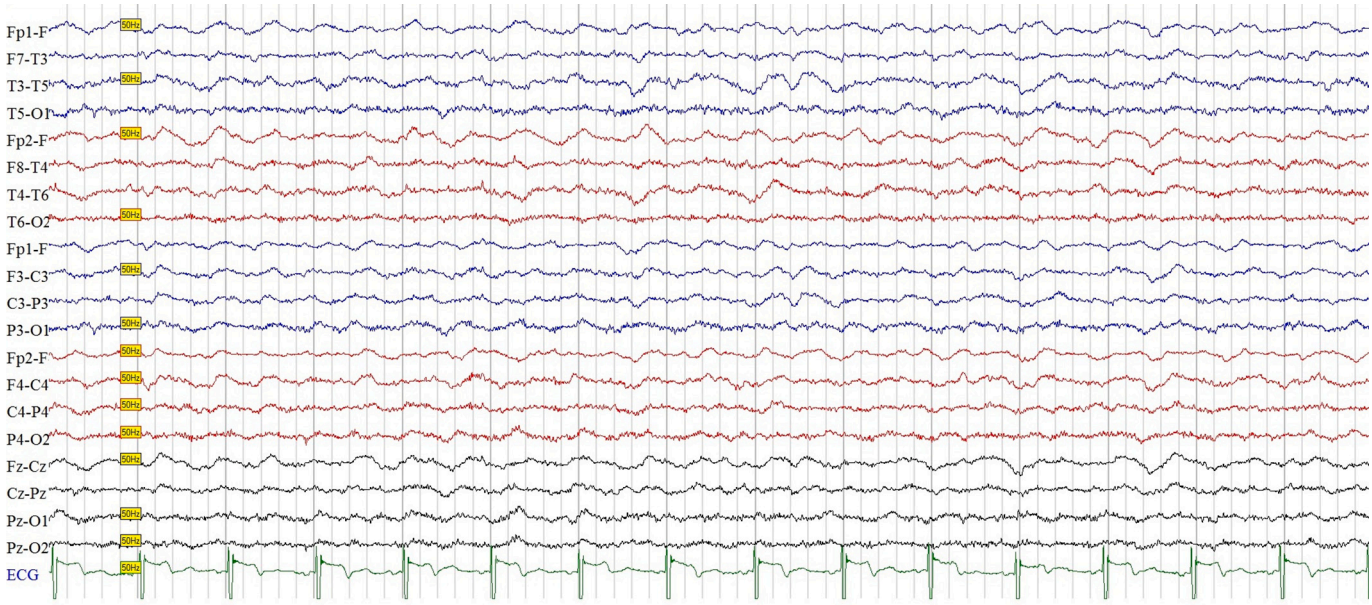

Fig. 2. Interictal EEG showing a moderate slowing of cerebral background with no evidence of epileptiform discharges.

was negative. Brain MRI showed a subtle increase in the signal on FLAIR images at bilateral hippocampi and insula that was correlating with postictal changes (Fig. 1). The patient was admitted and developed two more episodes of generalized tonic-clonic seizures that were aborted with diazepam. She was started on a loading dose of levetiracetam 1 g with a maintenance dose of 500 mg twice daily along with phenytoin 100 mg three times daily. The patient continued to have generalized tonic-clonic seizures requiring an increase in levetiracetam dose to 750 mg twice daily and adding lacosamide at 50 mg twice daily. Interictal electroencephalogram (EEG) showed moderate slowing of the cerebral background with no evidence of epileptiform discharges (Fig. 2). Continuous video EEG was not performed due to unavailability. Cerebrospinal fluid analysis showed normal cell count, normal protein at 0.31 g/L, elevated glucose at 4 mmol/L, and negative microbial cultures and serological tests. The patient continued to have seizures despite being on three antiepileptic medications necessitating admission into the intensive care unit where she was intubated and started on midazolam and propofol to induce a deep coma to abort her refractory seizures. COVID-19 PCR was repeated and came back negative. The doses of antiepileptic medications were optimized and she was started on pulse steroid therapy for five days followed by two sessions of plasma exchange on alternate days. The patient improved dramatically and was extubated after the immunotherapy. She remained seizure-free and was discharged after a total of three weeks of hospital stay. Her discharge medications were levetiracetam 750 mg twice daily, phenytoin 100 mg three times daily, and lacosamide 50 mg twice daily with a plan to gradually taper the antiepileptic medications. The patient was seen one week after discharge for follow-up where she was complaining of drowsiness, imbalance, concentration difficulty, and hand tremors most likely attributable to antiepileptic medications. Another follow-up after 4 weeks showed satisfactory improvement of her symptoms, and antiepileptic medications were gradually tapered.

3. Discussion

The outbreak of COVID-19 infection as a serious emerging disease

was accompanied by a host of neurological complications in up to 30% of hospitalized patients. The wide spectrum of neurological complications includes cranial neuropathies with anosmia and dysgeusia, meningitis, encephalitis, stroke, cerebral venous sinus thrombosis, encephalopathy, and Guillain-Barre syndrome.(Koralnik and Tyler, 2020) In addition, seizures and status epilepticus were reported in patients with COVID-19 infection. Seizures may either be primary or secondary to ischemic or hemorrhagic strokes, increased oxidative stress, electrolyte imbalance, and mitochondrial dysfunction.(Nikbakht et al., 2020)

The ChAdOx1 nCoV-19 vaccine is a viral vector vaccine that uses the modified chimpanzee adenovirus ChAdOx1 as a vector.(Ramasamy et al., 2021) More than 34 million vaccine doses were administered in Europe. The safety profile of the vaccine is good with commonly reported mild side effects such as injection-site pain, nausea, and headache, which usually resolve within a few days.(Hunter, 2021) The vaccine was linked to severe thrombotic events secondary to the production of rogue antibodies against platelet factor-4 resulting in massive platelet aggregation leading to cerebral venous sinus thrombosis that could potentially manifest as seizures.(Ledford, 2021) Seizures or status epilepticus following this vaccine were not previously reported in the literature.

The only speculated mechanism underlying the development of seizures after vaccinations in the literature was a vaccination-induced fever that acts as a seizure trigger.(Lu et al., 2021) However, our patient was a healthy non-epileptic nurse who developed NORSE as a first presentation only ten days following the first vaccine dose. This makes the fever theory less likely and prompts the search for more integral mechanisms related to the role of pro-inflammatory cytokines in the pathogenesis of post-vaccination epilepsy.

Angiotensin-converting enzyme 2 (ACE2) provides the access point of entry for coronaviruses, and ACE2 receptors are present in the brainstem to mediate the regulation of supranuclear cardiovascular and respiratory functions. Like other coronaviruses, COVID-19 can gain direct entry to the brain via the olfactory tract by antegrade axonal transport.(Steardo et al., 2020) Direct entry of viral particles into the brain can induce the microglia to initiate a storm of pro-inflammatory cytokines that includes TNF-α, IL-6, IL-1B along with prostaglandin E2, nitric oxide, and free radicals.(Huang et al., 2020) We are proposing that the viral vector vaccine may access the cerebral neuronal pathways to replicate the mechanism of seizures in patients with the real COVID-19 infection. The plausible mechanism for seizures is that the inflammatory cascade would conceivably result in neuronal hyperexcitation and subsequent seizures.

We are admittedly aware of the lack of a biological marker to establish causality between seizures and the vaccine. However, we cannot ignore the dramatic temporal association between recieving the vaccine and developing a florid status epilepticus in a previously healthy nurse. Moreover, the emergence of refractory status epilepticus failing four antiepileptic drugs with dramatic improvement only to autoimmune therapy dictates some respect to the instinctive logic of a concievable association between the vaccine and epilepsy. Finally, while causality is not confirmed, this case should certainly invoke further research to look for any potential pathogenic mechanism at a deeper and more molecular level.

4. Conclusion

We report a rare case of NORSE after the first dose of the ChAdOx1 nCoV-19 vaccine. We attribute the occurrence of NORSE to the vaccine due to the temporal relationship and the lack of risk factors for epilepsy in the patient. This report adds to the literature a possible rare side effect of a COVID-19 vaccine and contributes to the extremely limited literature on potential neurological side effects of viral vector vaccines. Healthcare providers should be aware of the possibility of post-vaccination epilepsy. The patient had recurrent seizures that were refractory to conventional antiepileptic drug therapy with a dramatic response to immunotherapy with pulse steroids and plasmapheresis. This likely reflects an underlying autoimmune mechanism in the genesis of post-vaccination generalized seizures without fever. Further research is needed to probe and study the exact mechanism at a more molecular level.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

References

Dong, E., Du, H., Gardner, L., 2020. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect. Dis. 20 (5), 533–534.
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395 (10223), 497–506.
Hunter, P.R., 2021. Thrombosis after covid-19 vaccination. BMJ 373, n958.
Koralnik, I.J., Tyler, K.L., 2020. Covid-19: a global threat to the nervous system. Ann. Neurol. 88 (1), 1–11.
Ledford, H., 2021. How could a COVID vaccine cause blood clots? Scientists race to investigate. Nature. 592 (7854), 334–335.
Li, Y.-D., Chi, W.-Y., Su, J.-H., Ferrall, L., Hung, C.-F., Wu, T.-C., 2020. Coronavirus vaccine development: from SARS and MERS to COVID-19. J. Biomed. Sci. 27 (1), 104.
Lu, L., Xiong, W., Mu, J., et al., 2021. The potential neurological effect of the COVID-19 vaccines: a review. Acta Neurol Scand. 144, 3–12. Published online March 29.
Nikbakht, F., Mohammadkhanizadeh, A., Mohammadi, E., 2020. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord. 46, 102535.
Ramasamy, M.N., Minassian, A.M., Ewer, K.J., et al., 2021. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 396, 1979–1993.
Steardo, L., Steardo, L., Zorec, R., Verkhratsky, A., 2020. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol (Oxf). 229 (3), e13473.
Zhu, N., Zhang, D., Wang, W., et al., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382 (8), 727–733.